REMARKS

Claims 38-51 and 60-73 are pending in the present application. New Claims 74-77 have been added. Support for the new claims can be found throughout the specification and claims as originally filed, for example, on page 6, lines 22-28; page 22, line 5 to page 23, line 6; and original Claim 4 of priority application no. 09/380,534, filed on September 1, 1999, which was incorporated by reference in its entirety into the instant application. Thus, no new matter has been added to the application by entering this amendment.

Applicants respectfully disagree with the rejections set forth in the Office Action mailed July 6, 2004, and provide the following remarks in response thereto. Applicants respectfully submit that the application is in condition for allowance.

Rejection Under 35 U.S.C. § 102

Claims 38-40, 45-47, 49-51, 62-64, and 68-69 were rejected under 35 U.S.C. § 102(b) as being anticipated by Sadao *et al.*, translation of Locoregional Immunotherapy-Topics at the 13th and 14th Meetings of the Japanese Research Society for Surgical Cancer Immunology, *Biotherapy* 9(7):845-851 (1995) (Sadao).

Respectfully, Applicants disagree with the instant rejection under § 102 in view of Sadao and assert that Sadao does not anticipate the claims. Applicants request reconsideration and withdrawal of the rejection in view of the following arguments:

(1) The Office Action misapplies, mischaracterizes and misinterprets the disclosure of Sadao;

(2) Sadao does not expressly or inherently anticipate any of the claims;

(3) The claims have been reconstructed using impermissible hindsight; and

(4) Sadao is a non-enabling reference because it does not teach how to perform the claimed methods.

The Disclosure of Sadao is Misapplied, Mischaracterized And Misinterpreted

Overview of General Content and Structure of Sadao:

Sadao is a 1995 review publication that purports to summarize 70 independent presentations from a two-year period. Sadao is organized into separate sections, outlined as follows:

- Abstract (page 2)
- Introduction (pages 2-3)
- Specific Immune Mechanisms (pages 4-9)
- Nonspecific Immunomechanisms (pages 9-11)
- Suitably Choosing a Drug Delivery System for Contact Between Effector Cells and Cancer Cells with High Efficiency (pages 11-12)
- Direct Locoregional Immunotherapy Using Cytokines (page 12)
- Immunostimulants Studies (pages 13-14)
- Cancer Treatment Using Monoclonal Antibodies (MoAb) (pages 14-15)
- Conclusion (pages 15-17)

As shown above, the different sections generally deal with distinct areas of research. Furthermore, review of Sadao reveals that the discrete sections are fragmentary in their reporting the 70 presentations. A discussion in one section does not correspond to a discussion in another section. As such, Sadao is not directed to a single technology or embodiment. Not surprisingly, Sadao does not provide consistent, unified, detailed or enabling teachings of any of the procedures reported in the individual presentations, but provides a general overview of their results. Sadao is thus not a "single reference" of the sort on which a rejection under § 102 can properly be based. Only by patching together various fragments of unrelated research results reported in different sections of Sadao, has the Examiner even *arguably* found some of the claim limitations.

The Federal Circuit has refused to find anticipation where a district court had combined disparate sections of single paper in order to find anticipation. *See Ecolochem, Inc. v. Southern California Edison co.*, 227 F.3d 1361, 1368-9 (Fed. Cir. 2000). In *Ecolochem* the Federal Circuit found that the district court misconstrued the allegedly anticipatory reference, erroneously linking one textual passage describing a particular method, with a later-described textual passage focused on different method. Respectfully, similarly here, the Examiner has erroneously linked textual passages pertaining to different research findings in order to try to piece together all of the elements of an individual claim.

The generalized overview and summaries disclosed in Sadao do not anticipate the instant claims. As discussed more fully below, the Examiner argues that the claims are anticipated by allegedly finding a combination of the claim elements in several of various unrelated and discrete sections, rather than as part of a single embodiment or technology. Respectfully, the elements of the claims are not present in Sadao, and the combination of cited teachings relied upon by the Office Action have been misapplied.

Summary of the Office Action Assertions:

Respectfully, the Examiner has seriously misunderstood or mischaracterized Sadao, and has therefore misapplied this reference in rejecting the claims. According to the Examiner, Sadao teaches a method of inducing a CTL response in a mammal by administering an antigen such as OK-432 obtained as a component of a microorganism or a by administering a tumor antigen such as MAGE-I (citing page 4) by injecting directly into the lymph nodes (citing the Abstract, page 13, and page 3). The Examiner further asserts that the antigen is delivered by indwelling reservoir or intermittent replacement administration directly to the lymph node (citing page 11, line 7 from the bottom). In addition, the Examiner asserts that the reference method inherently induces cytotoxic T lymphocytes independent of immunopotentiator. Also, the Examiner argues that Sadao teaches detecting the sustained CTL response by measuring the reduction in tumor metastasis (citing page 13, line 7) or CTL assay (citing page 8). Applicants respectfully disagree with these characterizations of Sadao.

Rebuttal of the Office Action Assertions:

Contrary to the Office Action, Sadao does <u>not</u> disclose the administration of MAGE-I polypeptide directly into the lymph nodes or any other lymphatic organ or vessel. MAGE-I is discussed on page 4 of Sadao in the section on Specific Immune Mechanisms. MAGE-I is discussed because, at the time of the article, it was one the few known cancer specific antigens ("there are very few tumors where a cancer-specific antigen has been identified, such as MHC class I restrictive MAGE-I in lung cancer and melanomas."). Sadao does <u>not</u> describe the administration of the tumor antigen MAGE-I to any region of an animal, much less to a lymph node or to the spleen.

Also in contrast to the assertions in the Office Action, Sadao does not disclose a method of inducing CTL by administering an "antigen," such as biological response modifier (BRM), OK-432, directly into the lymph nodes. The Examiner relies upon various passages to support the argument that Sadao teaches a method of inducing a CTL response by administering OK-432. The passages relied upon by the Examiner do not support the instant rejection. The passages have been taken out of order and out of context.

For example, the Examiner argues that Sadao teaches delivering antigen directly to a lymph node based upon the disclosure found in the Abstract, on page 13 (section on Immunostimulants Studies) and on page 3 (Introduction section) of Sadao.

However, the Abstract is not at all clear as to what was delivered into lymph nodes, or whether any CTL induction occurred. The Abstract recites:

> Seventy papers concerning the subject of locoregional immunotherapy for two years starting from the 13th Meeting of the Japanese Research Society for Surgical Cancer and Immunology were presented. The subjects were head and neck cancer, breast cancer, lung cancer, gastric cancer, liver cancer, colon cancer, peritonitis carcinomatosa, and the like in humans, and experimental animal tumors. The methods for administering BRMs were injection into the tumor or into lymph nodes, or into the hepatic artery or portal vein, etc. So-called missile therapy using monoclonal antibodies for various BRMs (immunostimulants, such as OK-432, PSK and lentinan, and cytokines, such as IL-2, TNF and IFN-γ) were reported. Various attempts based on remarkable advancements in cancer immunotherapy, and recently in molecular biology have been reported to this day.

As shown above, the abstract does not specify where any particular BRM is delivered, and what results were seen because of the delivery. No CTL induction is mentioned. Further, as discussed more fully below, those of ordinary skill in the art do not consider BRMs to be "antigens." Thus, the abstract does not support the assertions from the Office Action regarding antigen delivery and CTL induction. The abstract fails to disclose all of the elements of any independent claim.

The Examiner also points to part V of Sadao on page 13, which is entitled "Immunostimulants Studies." Under the second paragraph of this section, Sadao describes immunostimulatory action caused by the administration of BRM, OK-432, into lymph nodes as opposed to subcutaneous administration, and describes the reduction in liver metastasis by administration of OK-432 into the spleen. Even if delivery of a BRM were the equivalent of delivering an "antigen"--which, as set forth in detail below, it is not--still, CTL induction and

sustenance is not described anywhere in this section or in the paper in connection with the discussion of delivery into lymph nodes and the spleen. This is not surprising, as BRM administration is characterized, not by induction of CTL against the BRM, but instead by non-specific stimulation of the overall immune response. In fact, on page 3 Sadao characterizes OK-432 as an immunostimulant. Furthermore, with regard to the use of OK-432, nowhere does Sadao discuss the induction or sustaining of CTL for OK-432, for example.

Furthermore, the Examiner relies upon the introductory section of the paper found on page 3 to support the assertions in the Office Action. The introduction generally introduces the content of the paper, that being, a review of 70 presentations concerning the subject of locoregional immunotherapy. Page 3 does mention that the "routes of administration of local therapies were administration into the tumor or the lymph nodes, infusion into the hepatic artery or portal vein, etc." However, page 3 does not specify whether the described routes of administration delivered anything that would be considered an antigen. Regardless of what was delivered to the lymph nodes, Sadao provides no discussion of CTL induction or sustenance in connection with the lymph node delivery.

Also, page 3 states that "[s]o-called missile therapies using BRMs that are being used (immunostimulants, such as OK-432, PSK and lentinan; cytokines such as IL-2, TNF and IFN-γ) and monoclonal antibodies were reported." Sadao on page 3 does not specify where these substances are delivered, nor does it mention CTL induction. Furthermore, as discussed more fully below, substances classified as BRMs generally are not considered to be antigens in accordance with the instant claims by those of skill in the art. Sadao is consistent with that understanding. For example, Sadao lists OK-432 as a BRM and classifies it as an immunostimulant. Sadao classifies lentinan and PSK, which are mushroom extracts (shiitake mushroom and kawaratake mushroom), as immunostimulants. Also, Sadao classifies interleukin-2 and TNF-alpha as cytokines. Again, Sadao on page 3 does not specify where these substances were delivered and whether CTL were induced as a result.

Another misapplication of Sadao is the assertion in the Office Action that Sadao describes delivery of the antigen by indwelling reservoir or intermittent replacement administration as described on page 11 of Sadao (section entitled "Suitably Choosing a Drug Delivery System for Contact Between Effector Cells and Cancer Cells with High Efficiency").

Again, Applicants disagree and assert that the cited disclosure does not anticipate any elements of the claims. The cited passage generally summarizes the 70 presentations, some of which apparently described various drug delivery approaches. For example, Sadao describes "attempts at continuous administration of BRMs from an intraperitoneal indwelling reservoir in thermatology using CDDP. CDDP is also known as "cisplatin," which is a cytotoxic heavy metal that inhibits cell replication in a nonspecific manner. It is not clear from Sadao that any BRM or antigen was continuously administered to a lymph node by the indwelling reservoir.

Also, the passage on page 11 discussing intermittent replacement administration does not clarify what BRM, if any, was actually administered into the spleen. Furthermore, there is no disclosure of CTL induction in connection with the administration described on page 11.

With regard to CTL induction, the Examiner mischaracterizes Sadao, concluding that the method of Sadao "inherently induces cytotoxic T lymphocyte independent of immunopotentiator." Applicants strongly disagree. BRMs include substances that increase or stimulate immune responses, as well as substances that reduce or lessen immune responses. Accordingly, BRMs include substances that act as immunopotentiators, which stimulate the general immune response. Many of the specific BRMs described in Sadao, for example, OK-432, are classified as immunostimulants. Thus, the methods of Sadao actually utilize immunopotentiators, and therefore, the methods cannot be construed as inducing CTL independent of immunopotentiator.

Also, nowhere does Sadao describe CTL induction or sustenance in connection with delivery of an antigen to a lymph node or lymph vessel. Sadao does mention the delivery of the BRM, OK-432 to lymph nodes or the spleen. However, CTL induction is not described in connection with such delivery. Furthermore, as described below, one of ordinary skill in the art would not view Sadao as inherently inducing CTL.

The BRMs of Sadao Are Not Antigens:

In addition to the fact that Sadao is not a proper or adequate single reference for a § 102 rejection and requires a distorted reconstruction to cobble together certain of the elements of the claims, there is yet another weakness of this reference. The focus of Sadao is entirely on the administration of agents with biological response modifier activity (BRMs). However,

substances classified as BRMs are not considered "antigens" by those of ordinary skill in the art. The terms "antigen" and "BRM" are not synonymous. For example, attached as Exhibit 1 is an article by Goldwein *et al.*, entitled "Biological Response Modifiers," (http://www.oncolink.upenn.edu/treatment/article.cfm?c=2&s=9&id=54). In the article, BRMs are divided into three categories, (1) agents that restore, augment, or modulate the patient's normal immunological mechanisms; (2) agents that have direct antitumor effects; and (3) agents that have other biologic effects, such as interference with a tumor cell's ability to metastasize or survive after metastasis, promotion of cell differentiation, or interference with neoplastic transformation in cells. Several exemplary BRM agents are described: monoclonal antibodies, interferons, interleukin-2, colony stimulating factors and tumor necrosis factors. One of ordinary skill in the art will appreciate the distinction between such agents and antigens.

Further, to one of ordinary skill in the art, an antigen is a molecule that binds to the complementarity-determining region of a B cell or T cell antigen receptor (*i.e.*, an antibody or T cell receptor (TCR), respectively). In terms of the current paradigm of immunogenicity, an antigen provides "signal one" and of course, is the target of the immune response that is induced. BRMs on the other hand may bind to a variety of other receptors (*e.g.*, toll-like receptors, pattern-recognition receptors, or cytokine receptors) and provide "signal two." BRMs serve to increase (or decrease) the response which recognizes some other molecule(s), but BRMs are generally not themselves targets of the response. It should also be noted that some BRMs are not capable of interacting with MHC and being recognized by CTL. For example, some BRMs are made up of carbohydrate, rather than amino acids, and therefore, are not recognized by CTL.

A candidate BRM that induces a response against itself would be considered an undesirable BRM. Thus, the use of one term does not suggest the other to one of skill in the art due to the profound functional differences between antigens and BRMs.

In view of the above discussion Applicants disagree that Sadao anticipates the claims, because OK-432 is not considered by those of ordinary skill in the art to be an antigen. Because a BRM is not functionally interchangeable with an antigen, Sadao cannot be interpreted to teach administration of an antigen to induce a CTL response as required by the claims. Therefore, none of the claims is anticipated by Sadao, because Sadao does not disclose delivering an "antigen" according to the claims.

As discussed in the foregoing paragraphs, assertions made in the Office Action are based upon incorrect characterizations or interpretations of the disclosure of Sadao. The cited passages simply do not support the assertions made in the Office Action in support of the rejection under § 102. Respectfully, reconsideration and withdrawal of the rejection is requested.

Sadao Does Not Expressly Or Inherently Anticipate The Claims

Sadao Does Not Expressly Teach Each and Every Element of the Independent Claims:

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986).

Respectfully, Sadao fails to disclose each and every element of the claims.

Claim 38

Even with the strained and improper application of Sadao, not all of the claim elements are found in Sadao. For example, Claim 38 recites, *inter alia*:

> delivering a liquid comprising an antigen directly to a lymph node or lymph vessel of the mammal at a level sufficient to induce a CTL response in the mammal; and
>
> maintaining the antigen in the mammal's lymphatic system over time sufficient to induce the CTL response.

As discussed above, Sadao does not disclose delivering an "antigen" directly to a lymph node or lymph vessel. Furthermore, Sadao does not disclose delivering the antigen at a level sufficient to induce a CTL response in the mammal, because there is no CTL response shown in connection with delivering any antigen. Furthermore, there is no disclosure in Sadao of maintaining "antigen," and likewise, no maintaining antigen at a level sufficient to induce a CTL response. Therefore, Sadao does not anticipate independent Claim 38 or any claim that depends from it, because Sadao does not teach each and every element of independent Claim 38.

Claim 45

Independent Claim 45 recites, in relevant part:

> delivering a liquid comprising an antigen in a continuous, repeated, or sustained manner directly to a lymph node or lymph vessel of the mammal at a level sufficient to induce a CTL response in the mammal; and

maintaining the antigen in the mammal's lymphatic system over time sufficient to induce the CTL response.

As discussed above, Sadao does not disclose delivering an "antigen." It also does not disclose delivering an antigen in a continuous, repeated, or sustained manner directly to a lymph node or lymph vessel, or "at a level sufficient to induce a CTL response." Again, Sadao fails to disclose any CTL induction in connection with delivering a BRM or anything considered an antigen. As discussed above, Sadao also does not disclose maintaining antigen in the lymphatic system according to the claim. This is not surprising in view of the nature of Sadao as a general summary of 70 different presentations, which includes very little, if any, specific detail.

Sadao Does Not Inherently Anticipate the Independent Claims:

As set forth in § 2112 the M.P.E.P., "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

One of ordinary skill in the art would not view the method of Sadao as inherently inducing CTL because the so-called methods described in Sadao would not necessarily and always result in the induction of CTL. As explained more fully below, BRMs act to boost, direct, or restore the body's normal immune (defense) system. For example, they may help recruit various immune cells. One of skill in the art recognizes that a good BRM does not induce CTL against itself. If it did, it would be ineffective as a BRM. OK-432, which the Examiner argues is an antigen disclosed in Sadao as being delivered according to the claimed methods, is known in the art as a good BRM. As such, its delivery would not inherently anticipate the claims because delivery of OK-432 (or any other good BRM) would not *necessarily and always* induce

CTL, including CTL specific for the BRM. On the contrary, delivery of any good BRM, such as OK-432, would be expected by those of skill in the art to *rarely or never* result in a CTL response against the BRM. Sadao was interested in immunotherapy aimed at fighting cancer, not *Streptococcus*, from which OK-432 is derived. OK-432 was delivered as a BRM in order to intensify and boost the overall immune response against cancer cells and tumors, not to elicit CTL against OK-432. Therefore, delivery of OK-432 or any of the other BRMs does not inherently anticipate, because such delivery would not *necessarily and always* induce or sustain CTLs. Because the standard for inherency is not *rarely or never*, this inherency rejection is improper and must be withdrawn.

The Examiner Has Attempted To Reconstruct The Claims Using Impermissible Hindsight

The Examiner has patched together various fragments of unrelated research results reported in different sections of Sadao with the benefit of impermissible hindsight to reconstruct the limitations of the claims. This is evidenced by the above discussion, which shows that the Examiner has (1) utilized a reference that is inappropriate as a "single" reference under § 102; (2) taken passages out of order and out of context from the reference; (3) found claim limitations that plainly are not found in the reference by mischaracterizing and/or misinterpreting the reference; and (4) inappropriately equated BRMs with antigens. Absent hindsight, it is likely that Sadao never would have been relied upon as a 102 reference.

Sadao Does Not Anticipate Because It Does Not Enable The Claims

In addition, Sadao does not anticipate the Claims as asserted by the Examiner, because Sadao fails to enable one of skill in the art to perform the claimed methods.

A claim can only be anticipated by a reference if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996); *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education and Research*, 346 F.3d 1051 (Fed. Cir. 2003) ("To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate." "Enablement requires that 'the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation.'"); *Amgen, Inc. v*

Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 (Fed. Cir. 2003) ("A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled."); *PPG Industries, Inc. v. Guardian Industries Corp.*, 75, F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention.").

Recently, the Court of Appeals for the Federal Circuit reversed and remanded a district court summary judgment finding the claims invalid under 35 U.S.C. § 102 because the district court failed to consider whether the cited prior art reference was enabling. *See Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education and Research*, 346 F.3d 1051 (Fed. Cir. 2003) (decided October 2003). The district court had determined that the claims were inherently disclosed by the prior art reference, and therefore, were invalid under § 102. *See id.* However, the Federal Circuit reversed that finding of invalidity under § 102 stating that the issue was "more properly characterized as enablement arguments rather than inherency arguments." *Id.* Thus, the Federal Circuit stated that "[t]o serve as an anticipating reference, the reference must enable that which it is asserted to anticipate." *Id.*

Sadao does not provide details of the various experiments and procedures that were summarized, but merely provides general summaries of the presentations. This is not surprising in view of Sadao being a summary or review article of 70 different presentations, which lacks any specific detail. Here, for example, the Office Action states that Sadao anticipates because it discloses a method that inherently induces cytotoxic T lymphocytes independent of immunopotentiator. Claim 46 recites, "wherein induction of cytotoxic T lymphocytes is obtainable independent of immunopotentiator." Applicants assert that Sadao does not appear to disclose any methods that do not include the use of immunopentiating substances, and therefore does not enable any such methods. As such Sadao does not anticipate Claim 46 because it does not teach how to perform the claimed method. Therefore, Sadao does not teach how to perform the claimed method of Claim 46, and therefore is an improper, non-enabling reference under § 102.

Conclusion

The foregoing discussion establishes that Sadao is not a proper or adequate reference on which to base a rejection of the claims under § 102. The disparate nature of the "elements" in the

Sadao reference can only be selected and combined through a completely impermissible act of hindsight reconstruction of the claims. Furthermore, Sadao fails to enable one of skill in the art to perform the claimed methods. Applicants therefore respectfully request that all rejections based upon Sadao be withdrawn.

In light of the foregoing, Applicants respectfully submit that Claims 72-74, 77-84, 87, and 89-91 are not anticipated by Sadao because the reference does not teach each and every element of the independent claims. Accordingly, Applicants hereby request that the rejection under this section be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 38, 43, 45-46, 48, 65-66, and 70 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 6,204,250 B1 (of record, March 2001), Coupey *et al* (Cytokine 5(6): 564-9, November 1993) and Zinkernagle *et al* (Immunol Rev 156: 199-209, April 1997).

Claims 38, 45 and 60-61 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 5,830,452 A (1998) and U.S. Patent No. 5,279,608 (1994).

In addition, Claims 38, 45, 65-67 and 70-72 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 5,853,719 (filed April 30, 1996).

Finally, Claims 38, 41, 42, 45 and 73 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 5,766,601 (filed April 7, 1995).

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference(s) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The Examiner argues that the "antigen" of Sadao can be substituted with the respective antigens of the '250 patent, Coupey, and Zinkernagal. As discussed above in connection with the rejection under 35 U.S.C. § 102(b), Sadao alone does not anticipate the claims because Sadao does not teach each and every limitation of the independent claims. Also, none of the secondary

references alone discloses the deficient elements of the independent claims. Furthermore, the combination of Sadao with the secondary references still does not teach or suggest all of the claim limitations. Thus, the cited references, alone or combined, do not teach or suggest all the claim limitations. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

One of ordinary skill in the art would not be motivated to combine the references, as argued by the Examiner, to substitute Sadao's BRMs with the antigens of the secondary references. There is no basis or motivation to combine the references, as antigens and BRMs serve distinct purposes and are not interchangeable. Sadao summarized 70 presentations dealing with the use of BRMs. Sadao summarized presentations that explored attempts to improve therapies by stimulating or intensifying immune responses against tumors using BRMs. A person of skill in the art, considering the teachings of Sadao, would not be motivated to replace BRMs, which appear to stimulate the local immune reaction generally rather than specifically, with an antigen, because the antigen would not be expected to function as a good BRM. Thus neither the teachings of Sadao, nor those of any of the secondary references, can provide any motivation to make the claimed invention, nor can they provide any reasonable expectation of success in doing so.

Likewise, the combination of Sadao with the '452 patent and the '608 patent, still does not provide all of the elements of the claims. The computer-driven pump and the osmotic pump disclosed in the references do not provide the above-discussed elements that are missing from Sadao. Therefore, the claims are not obvious in view of the combination, even if made.

Also, the combination of Sadao with the '719 patent does not make Claims 38, 45, 65-67 and 70-72 obvious. One of skill in the art would not be motivated to use the vectors/cells of the '719 patent with the BRMs of Sadao. Even if there were a motivation to combine the references, all of the elements of the claims still are not present.

Finally, the combination of Sadao and the '601 patent does not render Claims 38, 41-42, 45 and 73 obvious. Even if there were a motivation to combine the references, all of the elements of the claims are not present. Furthermore, for reasons similar to those discussed above, Sadao does not suggest replacing its BRMs, which were intended to enhance the overall immune response, with the microorganisms of the '601 patent, which would not act similarly to the BRMs.

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Filed : **February 2, 2001**

Accordingly, Applicants respectfully submit that the PTO has failed to establish a *prima facie* case of obviousness due to its reliance upon Sadao as a primary reference. Thus, the claims are not obvious in view of the asserted combinations of references.

In light of the foregoing, Applicants respectfully submit that Claims 38, 41-43, 45-46, 48, 60-61, 65-67 and 70-73 are not obvious under 35 U.S.C. § 103. Accordingly, Applicants respectfully request that the rejection under this section be withdrawn.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding final Office Action have been addressed and that the application is in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain, or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: October 6, 2004

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